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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/479,997 06/07/95 ENGELHARDT

D ENZ-5 (D6) (C2)

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HM22/0530

EXAMINER

HOUTTEMAN, S

ART UNIT

PAPER NUMBER

1656

DATE MAILED:

05/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.
08/479,997

Applicant(s)

Engelhardt et al.

Examiner

Scott Houtteman

Art Unit

1656



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED _____ FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
- b) ☐ In view of the early submission of the proposed reply (within two months as set forth in MPEP § 706.07 (f)), the period for reply expires on the mailing date of this Advisory Action, OR continues to run from the mailing date of the final rejection, whichever is later. In no event, however, will the statutory period for the reply expire later than SIX MONTHS from the mailing date of the final rejection.

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on Jan 18, 2001. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will be entered upon the timely submission of a Notice of Appeal and Appeal Brief with requisite fees.
3. ☒ The proposed amendment(s) will not be entered because:
- (a) ☒ they raise new issues that would require further consideration and/or search. (See NOTE below);
- (b) ☒ they raise the issue of new matter. (See NOTE below);
- (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: See attached

4. ☐ Applicant's reply has overcome the following rejection(s): _____
5. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in separate, timely filed amendment cancelling the non-allowable claim(s).
6. ☒ The a) ☒ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: (see attached)
7. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
8. ☒ For purposes of Appeal, the status of the claim(s) is as follows (see attached written explanation, if any):
- Claim(s) allowed: NONE
- Claim(s) objected to: _____
- Claim(s) rejected: 454-575
9. ☐ The proposed drawing correction filed on _____ a) ☐ has b) ☐ has not been approved by the Examiner.
10. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
11. ☐ Other: _____

Item 3. NOTE:

Among the new issues raised by the 108 amended claims submitted after the final rejection:

Claim 454, for example, "directly or indirectly detected" raises new matter issues and new search/consideration issues for the "indirect" attachment;

Claim 476, for example, "Z" is now "HO-, monophosphate or diphosphate" raises new matter issues and new search/consideration issues for new side groups;

Claim 489 a delta position was changed to an alpha position; raises new matter issues and new search/consideration issues for new attachment;

Claim 494, for example, "sig" no longer "complexed" with a ferritin/binding protein conjugate but now is "a ligand" or "a specific ligand binding protein" raises new matter issues and new search/consideration issues

Claim 539 raises new 112, 2nd issues (as well as new matter issues) because x, y, and z are defined in two ways. mono-di- or triphosphates, "H- or HO-" in lines 8-13. But later in the claim when defining the SIG attachment site it appears that x, y and z and only be a phosphate: "Sig is covalently attached directly or through a chemical linkage to at least one phosphate selected from the group consisting of x, y and z." It is unclear whether SIG can attach to x, y and z when x, y and z are H- or HO- groups or if the definition of x, y and z was meant to change if a SIG moiety is attached.

Item 6:

The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:

The portions of the Agris Declaration which deal with the newly amended claims are moot in view of the non-entry of the amendment.

With respect to the new matter issue. The Agris Declaration states that no new matter issues are involved. Support is alleged for the claims 459-463. These claims recite (1) specific chemical linkages, (2) specific signal generating moieties and (3) specific points of attachment of the chemical linkages to the phosphate group.

The declaration attempts to find support for the claimed compound by first finding support for each of the three features separately. This argument is not persuasive. In mixing and matching distinct portions of the specification (some of which applicant felt were not relevant and has canceled from the specification) the Declaration fails to explain where the specification indicates that these portions must necessarily be combined in the way declarant proposes.

For example, a review of a passage about two linkages: "olefinic bond at the α -position," and " $-\text{CH}_2\text{NH}$ moiety" shows that these linkages are specifically proposed for attachment to the base. (The sentence beginning page 11, 2nd paragraph: "The linkage or group joining moiety A to Base B may include any of the well known bonds . . .") Nowhere in the specification does it suggest that these linkages should be attached to the phosphate. The Declaration does not explain how base linkages make phosphate linkages necessarily inherent.

The Declaration, it should be noted makes no mention of the fact that these passages are for base linkages and are not discussing linkages in general terms.

The new matter requirement is designed to prevent any further modifications of applicants invention after the filing date. Accordingly support must be either explicit or necessarily inherent in the specification. This is not the case here. The Declaration must do more than show that all of the pieces **can** be placed together to form the claimed subject matter. The Declaration must also show these pieces **must** be placed together to form the claimed subject matter because that is the most reasonable interpretation.

The Declaration also comments on page 26 on the originally filed claims, which required that "Sig" be attached only to the oxygen atom in the phosphate moiety. The newly presented claims are lacking this requirement. According to Declarant, "This missing element is not an essential or critical feature of the new claims as a whole because there is no specific requirement set forth in the specification that "Sig" be attached to the oxygen atom in the phosphate moiety.

This argument is not persuasive. First of all, the Declarant has just pointed out where in the specification it was required that Sig be attached to the oxygen atom. See for example original claim 141.

Secondly, the atoms present in a chemical compound must be considered a "critical element" of a claim to a chemical compound. They cannot simply be declared non-critical by applicant failing to recite specific requirements in the specification. The organic chemist would consider it critical to organic chemical compound the structure of that chemical compound, down to each and every atom. Furthermore, the reagents and reaction conditions are also critical.

Without this knowledge, in the specification or in the well known prior art, the organic chemistry could only guess about the structure of the compound and how it was made.

With respect to the enablement arguments in the Declaration. These arguments are not persuasive for reasons similar to those stated above. The Declaration fails to point out where the specification discloses attaching the claimed signal moieties to the phosphate group of a nucleotide. The Declaration only points out where the specification discloses attachment to the base group of a nucleotide.

The Declarant points to Example V as "a method of attaching biotin." Example V recites a method of Halloran. This is not persuasive in view of the fact that the Declarant also states "the protein in Halloran would not be considered "a detectable label." This argument is not persuasive. Proteins are detectable labels. They can be detected, for example, with radio labeled antibodies.

The Declarant points out "the Engelhardt Declaration Exhibit 6, the chemistry and reactions for attaching substituents to the oxygen or phosphorus atoms in a nucleotidyl phosphate or phosphoric acid moiety were already known in the art at the time the initial application was filed in June 1982.

However, the Declarant also points out that Stawinski et al. (one of the references in the Engelhardt Declaration) merely provided a starting point regarding possible reaction conditions that could be used. The references cited were primarily used as guidelines for trying to formulate methods for synthesizing oligonucleoside methylphosphonates." Thus the Declarant's own

interpretation of the Engelhardt Declaration references were not fully enabling but mere "starting points."

With respect to the Obviousness arguments, Declarant argues that Miller and Halloran and the state of the prior art does not render the invention obvious. This argument is not persuasive. The Declarant also states "as detailed on pages 11 and 12 in the Engelhardt Declaration, the chemistry and reactions for attaching substituents to the oxygen or phosphorus atoms in a nucleotidyl phosphate or phosphoric acid moiety were already known in the art at the time the initial application was filed in June 1982."

The Sig moiety "Biotin" was known in the prior art as a prosthetic group attached to protein. Other proteins were known at Sig moieties due to the fact that antibodies can specifically detect them. Halloran teaches the attachment of proteins to phosphate groups.

The Declarant argues that Halloran attaches protein to polynucleotides only for non-labeling purposes. (see Declaration page 30). This argument is not persuasive. These are product claims are not limited to any specific use. Since protein can be used as a label (detected, for example by an antibody) the claims read on the prior art.

Papers relating to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Technology Center 1600 Fax numbers are (703) 305-3014 and 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott Houtteman whose telephone number is (703) 308-3885. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday from 8:30 AM - 3:30 PM. The examiner can also be reached on alternate Wednesdays.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center receptionist whose telephone number is (703) 308-0196.

Scott Houtteman
May 29, 2001



**SCOTT W. HOUTTEMAN
PRIMARY EXAMINER**